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Variation in physico-chemical and bacteriological characteristics of dialysis water: a case study of eight hemodialysis centers

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ABSTRACT

Hemodialysis (HD) patients are exposed to large volumes of water and any contamination may cause potential health risks. A multicenter study was aimed at evaluating and comparing the physico-chemical, bacterial quality and endotoxin levels of dialysis water of eight HD centers consisting of seven in Algeria and one center in France. A total of 576 and 1,440 samples were examined for physico-chemical and bacterial analysis respectively and 192 samples for endotoxins, from April 2016 to March 2019. The results indicated that the dialysis water quality in some centers did not comply with the international standards for calcium, potassium, total and free chlorine, lead, cadmium, copper, and aluminum. Surprisingly, the conductivity was significantly higher than the allowed limits among all centers. Regarding the efficiency of the dialysis water treatment system, significant differences ($p < 0.05$) were recorded between tap water and dialysis water samples with the exception for cadmium in one of the centers where a low rejection rate of 8% was obtained. All removal rates were higher than 50% except for two participant centers. Total microbial counts at 22°C were present at levels higher than the maximum value of 100 CFU/mL in 75% of samples for one center while endotoxin levels were below the international standards (<0.25 IU/mL) in ≥65% of dialysis water samples. These data imply possible risks to hemodialysis patients and more efforts are needed to improve water quality management practices in dialysis centers. National standards for dialysis water should be developed.

Keywords: Hemodialysis; Dialysis water; Quality; Assessment; International standards

1. Introduction

Given the increasing incidence of chronic kidney disease (CKD) worldwide, the number of patients requiring treatment for end-stage renal disease (ESRD) is also growing [1]. More than 2.5 million patients have undergone renal replacement therapy and this number is estimated to hit 5.4 million by 2030 [2]. In Algeria, CKD accounts for 3.5 million medical admissions, most of which ended in ESRD [2,3]. Thus, ESRD is considered a major public health issue because of its medical and socio-economic consequences consisting of renal replacement therapy by dialysis or kidney transplantation.

Currently, the steady rise in the incidence of ESRD on the Algerian population and its complications reduce the quality of life and represent a major health concern with

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an estimated prevalence of 600 pmp (patients per million population) and an incidence of 200 pmp [2,4]. Among treatment practices, hemodialysis (HD) remains to date the principal and the most widely used method to help patients suffering from severe renal failure, far ahead of peritoneal dialysis and renal transplantation. During the last few years, the number of patients undergoing HD has increased worldwide [5]. A healthy individual ingests about 14 L of water per week [6]. In comparison during HD treatment, patients are dialyzed three times a week for approximately 3–4 h by session and receive large volumes of dialysis water (approximately 90–120 L) during a single dialysis session. According to the flow rate of the dialysate and the percentage of water discharged during the reverse osmosis (RO) process dialysis fluid volume reaches 580–860 L per week for HD patients. Guaranteeing dialysis fluid quality represents a crucial aspect of this type of therapy using large quantities for each patient [7].

Water represents 95% of the dialysate delivered to the dialyzer. It is considered an essential element for the efficiency and the biocompatibility of HD therapy [8]. The patient's blood is separated from this high volume of water by a thin dialyzer membrane limiting the transfer of contaminants according to their size, exposing subsequent patients to possible contamination. Feed water must therefore be treated by different processes such as particle filters, activated carbon, water softeners, deionizers, RO, ultraviolet light and bacterial filters to prevent the build-up of contaminants [6].

Given the relatively large volumes of water to which each patient is exposed repeatedly, it is crucial to guarantee the required quality of the dialysis fluid. This constitutes a vital aspect of safe HD, as chemical, bacterial and endotoxin contamination associated with bacterial debris can threaten the health of a patient requiring this treatment. In addition, HD patients often have additional comorbidities such as diabetes, hypertension, and cardiovascular disease, which make them more vulnerable to health complications [1]. Hence, the presence of these contaminants has a negative impact on the quality of life of patients with ESRD reflecting a significant contribution to morbidity and mortality [6].

The name of the water for HD purpose was codified by the 9th edition of the European Pharmacopoeia (EPh) as "Water for dilution of concentrated solutions for hemodialysis" and was considered as a medicine [9]. Thus, water treatment is crucial to ensure human health safety and well-being. Tap water is the principal source of water used in hemodialysis centers which is subjected to several pretreatments to eliminate any contaminants. Water contamination can lead to anemia, blood pressure diseases and acid-base balance disorders, neurological disorders, and bone disease. Consequently, patients on hemodialysis treatment may have acute or chronic issues that could lead to death [7].

Based on the literature data, contaminants can pose health risks even at low concentrations. Some substances may cause complications such as pyrogenic reactions and some can reach toxic concentrations, causing long-term physical damage while other substances are immediately toxic and can lead to death [7]. Chemical elements, bacterial contamination and associated endotoxins can seriously impact the health of HD patients. In addition, several authorized levels of chemical substances in drinking water, such as calcium, nitrate, sulfate, and chloramines are potentially hazardous to HD patients and may cause well-defined acute or chronic poisoning syndromes. High levels of calcium and magnesium, for instance, can lead to cardiovascular diseases. Furthermore, high levels of aluminum can also result in encephalopathy, bone disease and anemia.

Aiming to reduce patient exposure to potential contaminants, additional purification treatment is required for water used in HD. A series of purification processes such as deionization, carbon filtration and RO are generally employed to remove chemical contaminants. These processes also provide an effective barrier against microbiological contaminants [10]. Furthermore, in order to prevent patients from risks related to the use of contaminated water, a number of standards for the quality of HD water and fluid have been established such as EPh standards [9], International Organization for Standardization (ISO) (ISO 26722:2014) [11], American National Standards Institute (ANSI) and the Association for the Advancement of Medical Instrumentation (AAMI), (ANSI/AAMI 26722:2014) [12]. These standards and guidelines have been established to ensure the quality of water necessary to reduce chemical risks among patients under HD treatment.

Advancement of Medical Instrumentation represents the most widely used standards for the chemical and microbial quality of HD water [10]. To meet these standards, several purification steps are recommended to transform tap water into intravenous quality water. Tap water is not sterile and contains various pollutants, within acceptable limits, which makes it appropriate for human consumption but not for hemodialysis patients [13].

In the current multicenter study, the physical, chemical, and bacteriological characteristics and endotoxin levels of water used in HD was investigated. The goal was to prevent complications and toxicity and to ensure safety of HD patients. To the best of our knowledge, the present study is the first in Algeria and will provide a useful database to improve the quality and management of water used in HD centers. There are no Algerian standards for the quality of dialysis fluids. The standards established by the 9th edition of the EPh were used to compare results of the present study.

2. Materials and methods

2.1. Hemodialysis centers assessed

The physico-chemical, bacteriological quality and endotoxin levels of the water used for HD purposes in seven dialysis centers located in the north (4 centers), the west (3 centers) of Algeria, and one center in the north of France were investigated over 3 years period from April 2016 to March 2019. The centers were coded and identified as centers 1, 2, …, 8. The sampling was done every month, over a period of 3 years. During the study period, the sampling process was performed by collecting water samples from the entrance to the water plant (municipal water supplied) and from the exit of RO units. The water treatment system in each dialysis unit consisted of a succession of filtration, softeners, activated charcoal, and RO components.

2.2. Dialysis water treatment systems

All the dialysis centers were supplied by municipal tap water (feed water) for dialysis water production. The water treatment process involved several steps where the pretreatment step system responds to a classic scheme with passage of drinking water through 10 µm particulate filters, a sand filter, then through the resins of softeners to remove calcium and magnesium. After, the water passed through activated carbon filters to eliminate chlorine and its related compounds and through a microfilter 01 µm. This step was followed by RO containing a membrane made of modified polyamide thin film composite. The water distribution system of the HD units was made of polyvinyl chloride (PVC). All units had a single loop distribution system.

2.3. Physico-chemical sampling and analysis

A total of 576 water samples were collected monthly from the entrance of the dialysis water treatment system (municipal water that feeds each dialysis unit) and the exit from the RO (treated or dialysis water). All samples were collected in previously cleaned glass vials. Prior to taking the water sample to be analyzed, water was allowed to flow freely for 5 min through the outlets connected to the storage tank (before treatment) and the outlet valve (after treatment). Then the samples were transported to the laboratory within 1–4 h for analysis.

Chemical parameters were analyzed according to international standard methods ISO 23500:2011 [14]. pH and conductivity were measured using multiparameter meter (Multi 1970 I; WTW Inolab). Free and total chlorine were analyzed by the N,N-diethyl-p-phenylenediamine colorimetric method with DR/890 Colorimeter (HI96711C; HANNA). Nitrate and nitrite were measured by UV-Visible spectrophotometry (Jasco V-530 UV/VIS). Organic matter was determined by the permanganate index (permanganic oxidizability) method. The total hardness, calcium and magnesium were analyzed by the titrimetric method using ethylenediaminetetraacetic acid (EDTA). Spectrophotometry technique (Hach Lange; DR 6000) was used for sulfate, ammonium, and orthophosphate analysis while titrimetric technique (Mohr's method) for chloride ion determination. Sodium and potassium were analyzed using a flame photometer (Jenway®). However, fluoride ions were measured by potentiometry utilizing fluoride selective ion electrode (ELIT 8221F^- 41936). The trace elements, such as: aluminum, lead, total iron, copper, cadmium, and zinc, were determined by flame atomic absorption spectroscopy (Analyst 800; PerkinElmer). All samples were randomly collected, on different days, without any prior coordination with the staff of the dialysis centers.

2.4. Microbiological and endotoxin sampling and analysis

A total of 1,440 samples were collected monthly from five sampling points in the water treatment plant of all participant HD centers, including the dialysate that was obtained directly from all online monitors (dialysis machines) during sessions aiming at identifying any bacterial contamination. The following parameters were determined: total microbial counts (TMCs), at 22°C and 37°C, fecal coliforms, sulfite-reducing *Clostridium*, *Enterococcus*, total coliforms, and endotoxins. For microbiological analyzes the sampling points were the main water inlet (feed water), the outlet of the softener, the outlet of the RO system as well as the dialysate sampled from the online monitor (dialysis machine). All samples were analyzed according to the following bacteriological methods analysis: TMCs by incorporation into the medium [15], fecal coliforms, enterococci, sulfite-reducing *Clostridium* using membrane filtration method according to the International Standard Methods ISO [16,17], endotoxins by LAL-Test (*Limulus Amoebocyte Lysate*) (European Pharmacopoeia 9th ed 2017, gelation method 2.6.14) [9]. The dialysis fluid collection points for endotoxin analysis were as follow: the output of the RO system and the dialysate directly collected from the on-line monitor (dialysis machine). All 192 samples were collected every three months in sterile vials and transported to the laboratory using a portable cooler (4°C–6°C) and immediately analyzed.

2.5. Statistical analysis

Statistical analysis of data was performed using descriptive statistical tests such as mean, standard deviation, with Minitab Version 18.0 software. The conformity assessment data with the standards values was performed by means of the *z*-test for comparison with theoretical value (One sample *z*-test). A significant difference was examined between the analyzed parameters in raw drinking water and HD water using Student's *t*-test for two paired samples (paired *t*-test). Then the data was compared with those of EPh and AAMI standards. The normalization of data was tested using the Kolmogorov–Smirnov test using SPSS software version 23.0. Data were considered statistically significant when $p < 0.05$ with 95% confidence.

3. Results and discussion

The analysis results of the physico-chemical parameters are summarized in Tables 1 and 2 for tap water and HD water respectively with a comparison to national and international standards. The rejection rates appear in Table 3. Tables 4 and 5 as well as Figs. 1 and 2 present detailed results of the microbiological analysis at different points of sampling for all the studied centers.

3.1. Physico-chemical analyzes

The results (Table 1) of the tested parameters indicated an acceptable water quality in the most dialysis centers except for center 7 where a considerable level of free chlorine (12.259 ± 22.912 mg/L) was recorded significantly higher than Algerian standards for drinking water ($p = 0.002$). In centers 1 and 8, the chlorine amounts were also significantly ($p < 0.001$) elevated (0.31556 ± 0.11 mg/L) and (0.250 ± 0.139 mg/L) respectively. This contamination may have been due to intense chlorination of water stored in the tanks at the centers. Center 3 showed contamination by ammonium in the tap water (2.438 ± 8.155 mg/L) ($p = 0.041$). Regarding the levels of lead and cadmium, significant

($p < 0.001$) differences were found in center 1 compared with the standards (0.036 ± 0.022 mg/L), (0.063 ± 0.046 mg/L) respectively. This showed that the plant feed water is initially loaded with heavy metals. The presence of lead in drinking water maybe due to the corrosion of plumbing materials that contain lead, such as pipes, faucets, fittings, and solder. Exposure to lead in municipal water can cause brain and nervous system damage, behavioral problems, learning disabilities, and developmental delays (lead poisoning) [18]. Furthermore, there are many synthetic sources of cadmium in drinking water. The most common being corrosion of galvanized pipes, materials used in residential plumbing and drinking water distribution systems that can constitute another source of cadmium exposure. The major sources of cadmium include deterioration of pipes and, to a lesser extent, leaching of brass-based materials and cement mortar linings. Thus, exposure to high concentrations of cadmium in drinking water can cause gastrointestinal discomfort [19].

A strong relationship has been demonstrated between contamination of drinking water by trace elements and the incidence of chronic diseases such as kidney failure, liver cirrhosis, hair loss, and chronic anemia [20]. Knowing that the synthesis and structure of cellular components and transport of nutrients in the cells as well as the metabolism of the organism greatly depend on water, contaminated water by trace metals affects these biological processes and can lead to chronic and acute diseases specially for hemodialysis patients [21].

Regarding the other analyzed parameters, the average concentrations in the feed water were within the acceptable standards.

Table 2 summarizes the physico-chemical characteristics of treated water samples. Based on the conductivity concentration, there was a considerable decrease after water treatment as in center 1 where the mean values of conductivity were reduced from 783.4 ± 72.44 μS/cm to 14.76 ± 4.679 μS/cm. Findings across the centers ranged from a minimum of 14.76 ± 4.679 μS/cm to a maximum of 180.269 ± 232.312 μS/cm. Because there is no standard established by AAMI and EPh guidelines for conductivity, in our investigation these values were compared to French standards water dialysis. Findings reported here were significantly higher ($p < 0.001$) than the limit fixed at 4 μS/cm [22]. Identical results were reported in Palestine [23] where a study conducted in eight dialysis centers showed that conductivity levels were not within the allowed limits in all the centers. The results from the current work agree with those of an Iranian study conducted by Ali-Taleshi et al. [24] on 24 samples of treated water in two hospitals where high levels of conductivity of 14.21 ± 6.24 μS/cm and 293.5 ± 63.00 μS/cm were recorded. Z-tests showed a significant difference between concentrations of the measured free chlorine with AAMI standards at 95% confidence interval ($p = 0.014$) in center 7 with an average concentration of 1.216 ± 1.877 mg/L. These findings agreed with those obtained by Humudat and Al-Naseri [7] from four dialysis centers in Baghdad (Iraq). They reported that free chlorine exceeded the maximum level suggested by the AAMI standards by 13%, while total chlorine exceeded the EPh standard limit in centers 1 and 7 showing an average of 0.165 ± 0.05 mg/L and 1.575 ± 2.104 mg/L ($p < 0.001$). In addition, the concentrations of calcium were significantly ($p = 0.002$) higher than the standards in center 3 (3.492 ± 2.830 mg/L). This elevated concentration remained lower than that found by Braimoh et al. [6] who reported a very high deviation of calcium concentrations from the standard value (2 mg/L) ranging from 126 to 256 mg/L across six HD centers in Nigeria. Furthermore, an Iranian study carried out by Shahryari et al. [10] displayed average concentrations of calcium ranging from 6.75 to 19.3 mg/L exceeding the tolerated level of calcium in dialysis water. In addition, current findings revealed a concentration of potassium (7.08 ± 12.537 mg/L) which was higher than EPh standards in center 7 ($p = 0.01$). This result, which was unexpected in center 7, was comparable to that reported in the Nigerian study of Braimoh et al. [6] reflecting a lower mean potassium concentration, between 3.9 and 5.55 mg/L. These values were in compliance with the AAMI limits but did not meet the EPh standards, that is 2 mg/L while other studies [4,23] showed appropriate levels of potassium in dialysis water.

Aluminum concentrations exceeded the maximum level suggested by AAMI and EPh in center 2 with an average of 0.015 ± 0.017 mg/L ($p = 0.047$). This result is comparable to other studies such as that by Humudat and Al-Naseri [7] who reported higher concentrations between 0.01 and 0.05 mg/L while Braimoh et al. [6] showed a high level of aluminum in all samples analyzed in the range of 0.04–5.00 mg/L. In another multicenter study from Iran, values did not meet guideline standards in all participating dialysis centers [10]. It can be argued that the dialysis water treatment system itself could be a probable source of aluminum contamination, as the hot water used for thermal disinfection can dissolve the aluminum particles that make up the anode of the device. An aluminum water distribution pump may also be a source of contamination [25].

Other trace elements such as lead, cadmium and copper were present at high concentrations exceeding the values recommended by AAMI. The mean values of the concentrations were as follow: 0.029 ± 0.018 mg/L, 0.058 ± 0.125 mg/L and 0.203 ± 0.15 mg/L ($p < 0.001$, $p = 0.005$ and $p < 0.001$) respectively (Table 2). These findings are like those of some studies worldwide where authors noted elevated levels of these metals and non-compliance with international standards [6,10,23]. Recent papers [26,27] demonstrated an association between exposure to these trace elements and an increase in incidence and severity of kidney disease. Therefore, it is crucial to control their amount in dialysis fluids to prevent the poisoning of patients with toxic metals.

Regarding the efficiency of the dialysis water treatment process (Table 3), significant differences ($p < 0.05$) were recorded between tap water and HD water samples across the different dialysis centers except for cadmium in center 1 where a low rejection rate of 8% was obtained ($p = 0.397$). Unsatisfactory results were also observed, at this dialysis service, for fluoride, lead, copper, and total iron where the removal rates reached 40.5%, 18.7%, 22.8%, and 33.9%, respectively. For center 7, the percentage of sodium rejection was only 21.9%. However, the percentage of samples conforming to standards exceeded 80% in most centers, except for center 1 (73%), center 3 (73%), center 6 (65%) and center 7 (78%). It should be noticed that 39% of collected samples showed a rejection rate exceeding 90%, such as was the case of center 6

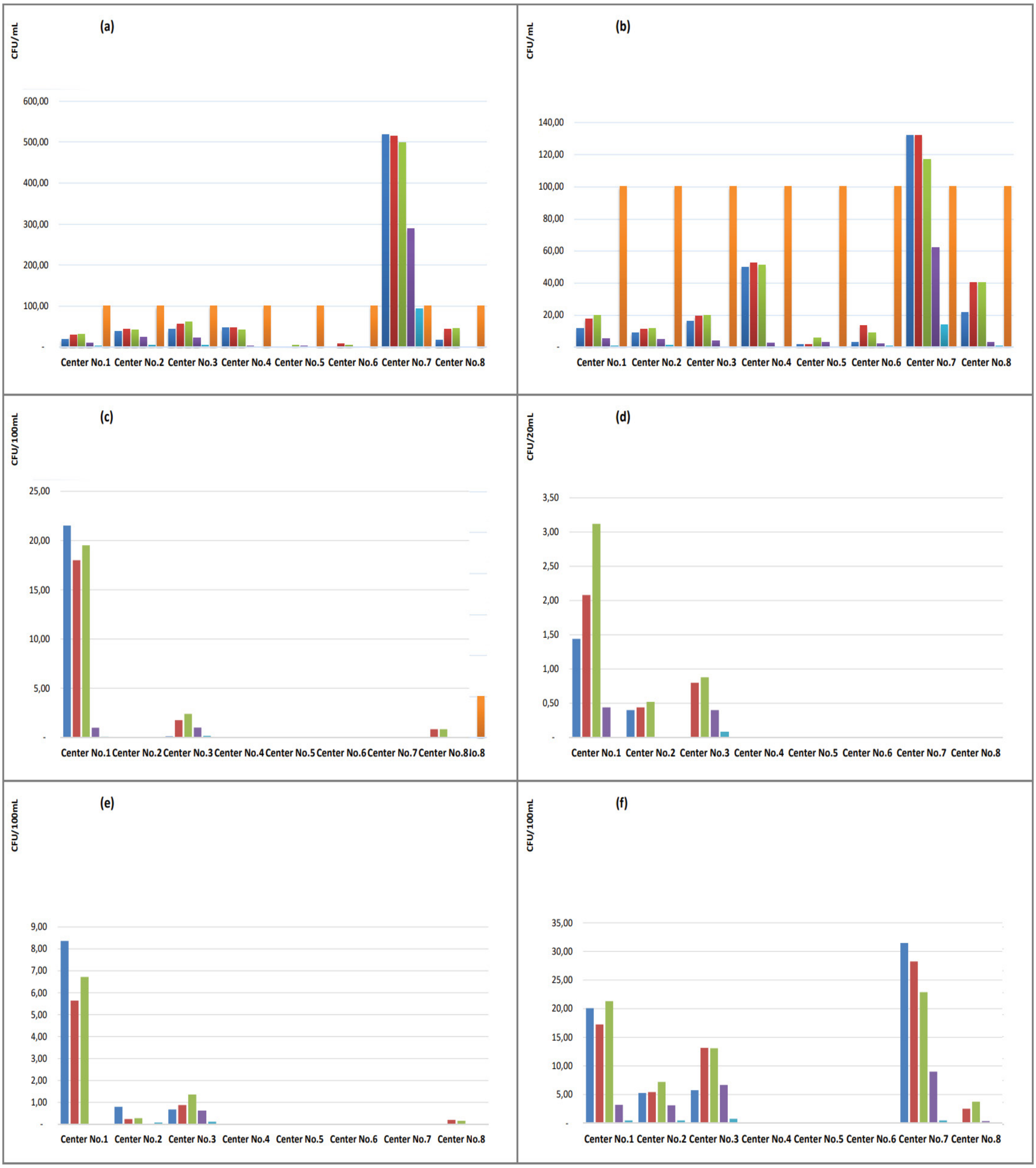

Fig. 1. Microbiological parameters for all the HD centers: (a) total microbial counts TMCs at 22°C, (b) total microbial counts TMCs at 37°C, (c) fecal coliforms, (d) sulfite-reducing *Clostridium*, (e) *Enterococcus*, and (f) total coliforms at different points of sampling: ■ Entrance of the water treatment plant, ■ Exit from the softener, ■ Exit from the reverse osmosis, ■ Online HD machine (dialysate), ■ Exit from the activated carbon filter, ■ EPh standards for HD water.

where the 13 chemical elements analyzed (56.5%) showed a rejection rate higher than 90% with total removal (100%) of the following parameters (free and total chlorine, nitrite, zinc, and copper). This qualifies this dialysis unit as the most efficient during study period. Center 4 comes next with 47.8% of the parameters exceeding 90% of removal rate. Despite the low rejection rates in some cases, the physico-chemical characteristics of RO-treated waters remained consistent with international limits in most dialysis centers [4,28,29].

3.2. Microbiological and endotoxin analysis

Referring to the microbiological analyses summarized in Tables 4 and 5, CFU values for municipal water in some centers did not meet standards as was the case of center 1 that displayed the largest amount of CFU for fecal coliforms (21.52 ± 14.88 CFU/100 mL), sulfite-reducing *Clostridium* (1.44 ± 1.69 CFU/100 mL), *Enterococcus* (8.36 ± 8.17 CFU/100 mL) and total coliforms (20.08 ± 13.64 CFU/100 mL). Also, center 7 showed elevated bacterial counts of TMC at 22°C and 37°C of 518.80 ± 188.82 and 132.20 ± 39.03 CFU/mL, respectively. Furthermore, bacterial contaminations at lower levels were registered in centers 2 and 3 when the other centers followed the international standards.

TMCs at 22°C were present at high level in treated water at center 7 (288.00 ± 132.07 CFU/mL) and exceeded the AAMI and EPh limits (<100 CFU/mL) ($p < 0.001$). The mean values of TMCs at 22°C in the dialysate were (92.96 ± 50.89 CFU/mL) and 75% of collected samples from center 7 showed several bacteria higher than the standards for TMCs. However, the results of the treated dialysis water and dialysate samples from the other seven centers in the study met the limits of AAMI and EPh. Compared to a recent study conducted by Morghad et al. [30] in Tlemcen in north-western Algeria, all water samples used for the preparation of dialysate were contaminated. The bacterial counts were as 118 and 182 CFU/mL for samples at the distribution loop and at the entry of dialysis machine respectively. Present findings were comparable to those found in Iran by Shahryari et al. [10]. The authors reported that 12.5% of dialysis water samples exceeded the EPh standards and all CFU values were below AAMI standards (<200 CFU/mL) in all samples among five dialysis centers over a 5-months period. Lower TMCs at 22°C and 37°C (1.0 ± 0.1 to 3.5 ± 0.57 CFU/mL respectively)were recorded in an Italian study in nine nephrology dialysis departments [28]. In Palestine, Abualhasan et al. [23] found that 12.5% of the dialysis centers showed microbiological contamination. Another research [31] from Brazil carried out in three hemodialysis units for 1 year reported fungal contamination in 24.1% of the dialysis water and dialysate samples. All these investigations concluded that bacterial contamination of dialysis fluids was a reality in different dialysis centers.

Fig. 1 illustrates the bacterial count through several points of the water treatment chain and dialysate of each center. The bacterial counts, detected in the water released throughout the activated carbon filter, were higher compared to those observed in water at the entrance, such the case of TMCs at 22°C and 37°C in all centers except center 7. Also, contaminations by fecal coliforms in centers 3 and 8, by sulfite-reducing *Clostridium* and *Enterococcus* in center 3 and by total coliforms in centers 1, 2, 3 and 8 were detected. These findings indicated that the softener and activated carbon filter as well as the dialysis machines constitute the preferred site for microbial proliferation, enabling the possibility of contamination of the treated water and the dialysate as it was reported by others [30–33]. Fig. 2 represents the percentage of satisfactory results for endotoxin levels with regard to AAMI and EPh limits (<2 IU/mL and <0.25 IU/mL, respectively). Data showed a compliance rate ranging between 65 to 100% for treated water and dialysate samples. It should be noted that center 8, located in France, showed the best endotoxin quality with 100% of samples in the limit (<0.25 IU/mL) followed by center 5 with 90% and 96% for HD water and dialysate respectively while the highest level of compliance recorded in center 6 was only 65% for treated water samples. Unsatisfactory results, related to endotoxin levels greater than 0.25 EU/mL were observed in 20.71% ± 8.50% and 15.86% ± 8.395% of dialysis water and

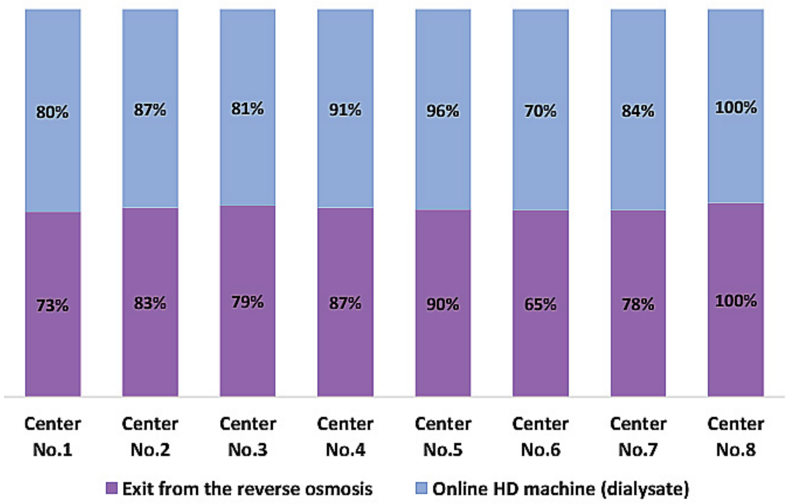

Fig. 2. Profile of satisfactory results for endotoxin levels.

Table 1
Physical and chemical parameters of municipal drinking water from the eight HD centers, in comparison to Algerian and French standards for drinking water

Parameters Mean ± SD	Algeria							France	Limits	
	Center No. 1	Center No. 2	Center No.3	Center No. 4	Center No. 5	Center No. 6	Center No. 7	Center No. 8	Algerian limits[a]	French limits[b]
pH	7.648 ± 0.148	7.734 ± 0.239	7.559 ± 0.227	7.998 ± 0.3663	7.672 ± 0.3472	8.004 ± 0.417	8.164 ± 0.2602	7.733 ± 0.133	≥6.5 and ≤9	6.5–8.5
Conductivity (µS/cm)	783.4 ± 72.44	1,126.361 ± 335.4	1,090.806 ± 490.2	826.898 ± 247.68	1,020.694 ± 70.74	950.139 ± 171.68	769.028 ± 150.652	555.333 ± 54.631	2,800	≥200 and ≤1,100
Free chlorine (mg/L)	0.3156 ± 0.11[c]	0.037 ± 0.032	0.028 ± 0.023	0.005 ± 0.009	0.009 ± 0.015	0.005 ± 0.01	12.259 ± 22.912c	0.250 ± 0.139	0.1	–
Total chlorine (mg/L)	0.3664 ± 0.106	0.069 ± 0.058	0.039 ± 0.03	0.013 ± 0.021	0.017 ± 0.025	0.001 ± 0.019	26.011 ± 42.081	0.347 ± 0.148	–	–
Chlorides (mg/L)	70.6 ± 86.820	258.186 ± 62.51	255.853 ± 141.7	170.213 ± 49.930	140.656 ± 42.903	122.99 ± 27.71	151.197 ± 63.403	67.3958 ± 22.063	500	250
Nitrite (mg/L)	0.0375 ± 0.027	0.0207 ± 0.014	0.109 ± 0.547	0.008 ± 0.004	0.005 ± 0.005	0.005 ± 0.006	0.006 ± 0.006	0.054 ± 0.093	0.2	0.5
Nitrate (as N) (mg/L)	11.274 ± 1.209	5.521 ± 3.763	5.830 ± 16.979	6.914 ± 17.049	6.399 ± 2.771	3.437 ± 1.732	7.008 ± 3.402	12.036 ± 8.369	50	50
Calcium (mg/L)	97.45 ± 24.116	71.63 ± 9.318	73.211 ± 44.247	68.367 ± 20.442	94.167 ± 12.367	92.083 ± 24.551	67.542 ± 11.598	75.025 ± 11.196	200	–
Magnesium (mg/L)	28.74 ± 15.967	39.753 ± 10.096	38.833 ± 20.820	14.998 ± 18.837	43.477 ± 7.390	26.578 ± 10.729	7.866 ± 4.323	16.801 ± 6.246	–	–
Total hardness (mg/L)	362 ± 22.335	311.383 ± 69.153	264.472 ± 105.703	231.0278 ± 102.503	414.333 ± 51.000	339.583 ± 97.334	200.663 ± 30.42	206.458 ± 13.231	500	–
Sulfate (mg/L)	43.62 ± 8.62	62.476 ± 16.983	73.856 ± 32.624	55.450 ± 8.714	52.761 ± 6.745	48.226 ± 7.126	73.194 ± 31.944	53.507 ± 6.714	400	250
Ammonium (mg/L)	0.007 ± 0.02	0.149 ± 0.158	2.438 ± 8.155[c]	0.048 ± 0.055	0.0314 ± 0.014	0.035 ± 0.015	0.044 ± 0.018	0.045 ± 0.015	0.5	0.1
Oxidizable substances (mg/L)	0.649 ± 0.701	1.198 ± 0.668	1.438 ± 0.771	1.279 ± 0.538	1.021 ± 0.372	0.686 ± 0.328	1.327 ± 0.965	0.738 ± 0.23	5	5
Sodium (mg/L)	165.314 ± 50.636	109.137 ± 28.31	105.809 ± 36.323	36.558 ± 11.424	14.094 ± 6.217	25.408 ± 6.79	57.744 ± 13.003	15.603 ± 28.05	200	200
Potassium (mg/L)	2.787 ± 2.632	4.269 ± 1.18	4.047 ± 1.844	1.606 ± 0.823	1.542 ± 0.943	1.720 ± 0.55	9.07 ± 13.153	1.310 ± 0.263	12	–
Orthophosphate (mg/L)	0.001 ± 0.004	0.047 ± 0.029	0.042 ± 0.027	0.019 ± 0.013	0.023 ± 0.019	0.008 ± 0.016	0.018 ± 0.014	0.153 ± 0.247	5	–
Fluorides (mg/L)	0.297 ± 0.125	0.315 ± 0.143	0.257 ± 0.12	0.095 ± 0.025	0.172 ± 0.093	0.191 ± 0.088	0.080 ± 0.02	0.483 ± 0.162	1.5	1.5
Aluminum (mg/L)	0.012 ± 0.01	0.064 ± 0.064	0.026 ± 0.058	0.042 ± 0.02	0.065 ± 0.027	0.038 ± 0.015	0.052 ± 0.019	0.026 ± 0.01	0.2	0.2
Lead (mg/L)	0.036 ± 0.022[c]	0.008 ± 0.006	0.009 ± 0.009	0.0003 ± 0.001	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.006 ± 0.003	0.01	0.01
Cadmium (mg/L)	0.063 ± 0.046[c]	0.001 ± 0.001	0.001 ± 0.001	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.002 ± 0.002	0.003	0.005
Zinc (mg/L)	0.025 ± 0.022	0.0294 ± 0.015	0.016 ± 0.014	0.019 ± 0.014	0.025 ± 0.018	0.021 ± 0.018	0.028 ± 0.015	0.02 ± 0.011	5	5
Copper (mg/L)	0.263 ± 0.175	0.317 ± 0.127	0.278 ± 0.158	0.023 ± 0.018	0.000 ± 0.000	0.006 ± 0.018	0.044 ± 0.032	0.193 ± 0.154	2	2
Total iron (mg/L)	0.034 ± 0.021	0.032 ± 0.016	0.042 ± 0.017	0.029 ± 0.01	0.040 ± 0.016	0.049 ± 0.022	0.175 ± 0.197	0.011 ± 0.003	0.3	0.2

[a]Official Journal of the Algerian Republic, N°13 (2014);
[b]Official Journal of the French Republic, NOR: SANP0720201A (2007);
[c]Significant differences between concentration of parameters with Algerian Standards for Municipal Drinking Water (*P*-value < 0.05).

Table 2
Physical and chemical parameters of HD water from the eight HD centers in comparison to Association for the Advancement of Medical Instrumentation (AAMI) standards and the 9th edition of the European Pharmacopoeia (EPh)

Parameters Mean ± SD	Algeria							France	Limits	
	Center No. 1	Center No. 2	Center No.3	Center No. 4	Center No. 5	Center No. 6	Center No. 7	Center No. 8	AAMI limits[a]	EPh limits[b]
pH	6.214 ± 0.432	7.47 ± 0.695	6.894 ± 0.604	6.913 ± 0.333	6.680 ± 0.190	6.805 ± 0.500	7.3474 ± 0.285	6.66 ± 0.472	–	–
Conductivity (μS/cm)	14.76 ± 4.679	56.850 ± 79.984	64.862 ± 71.067	15.706 ± 14.463	29.235 ± 15.691	58.839 ± 153.907	180.269 ± 232.312	28.940 ± 105.218	–	–
Free chlorine (mg/L)	0.188 ± 0.076	0.01 ± 0.015	0.007 ± 0.009	0.0006 ± 0.003	0.002 ± 0.005	0.000 ± 0.000	1.216 ± 1.877[c]	0.049 ± 0.061	0.5	–
Total chlorine (mg/L)	0.165 ± 0.05[d]	0.026 ± 0.026	0.013 ± 0.014	0.002 ± 0.005	0.006 ± 0.011	0.000 ± 0.000	1.575 ± 2.104[c]	0.078 ± 0.023	–	0.1
Chlorides (mg/L)	6.389 ± 6.931	3.911 ± 9.372	11.601 ± 16.406	6.656 ± 4.994	3.31 ± 2.930	2.488 ± 1.794	57.765 ± 37.68	1.829 ± 4.251	–	50
Nitrite (mg/L)	0.019 ± 0.023	0.005 ± 0.006	0.039 ± 0.199	0.001 ± 0.001	0.001 ± 0.001	0.000 ± 0.000	0.001 ± 0.001	0.03 ± 0.062	–	
Nitrate (as N) (mg/L)	0.793 ± 0.444	0.654 ± 0.653	1.012 ± 0.916	0.694 ± 1.022	0.371 ± 0.224	0.278 ± 0.145	0.601 ± 0.262	1.023 ± 3.483	2	2
Calcium (mg/L)	0.1542 ± 0.265	0.575 ± 1.152	3.492 ± 2.830[c,d]	0.642 ± 0.797	0.219 ± 0.3495	0.122 ± 0.261	2.089 ± 2.464	0.092 ± 0.013	2	2
Magnesium (mg/L)	0.114 ± 0.442	0.162 ± 0.539	2.313 ± 2.861	0.055 ± 0.123	0.025 ± 0.060	0.039 ± 0.083	2.275 ± 2.463	0.072 ± 0.058	4	2
Total hardness (mg/L)	0.723 ± 2.024	1.778 ± 4.342	9.625 ± 10.274	1.431 ± 1.564	0.639 ± 0.997	0.467 ± 0.952	14.581 ± 12.922	0.150 ± 0.071	–	–
Sulfate (mg/L)	0.63 ± 0.800	6.218 ± 17.961	14.205 ± 23.555	5.269 ± 4.497	0.950 ± 0.792	1.524 ± 1.371	27.179 ± 35.079	1.691 ± 7.058	100	50
Ammonium (mg/L)	0.003 ± 0.013	0.069 ± 0.045	0.136 ± 0.252	0.022 ± 0.014	0.011 ± 0.01	0.009 ± 0.012	0.019 ± 0.017	0.029 ± 0.035	–	0.2
Oxidizable substances (mg/L)	0.289 ± 0.326	0.483 ± 0.321	0.348 ± 0.221	0.279 ± 0.14	0.344 ± 0.179	0.193 ± 0.141	0.509 ± 0.3	0.299 ± 0.078	–	–
Sodium (mg/L)	0.325 ± 0.578	6.314 ± 9.347	18.197 ± 25.343	2.697 ± 1.504	2.369 ± 1.484	2.748 ± 1.898	8.436 ± 9.848	6.531 ± 25.93	70	50
Potassium (mg/L)	0.032 ± 0.096	0.284 ± 0.659	0.142 ± 0.26	0.021 ± 0.068	0.000 ± 0.000	0.013 ± 0.042	7.08 ± 12.537[d]	0.400 ± 0.047	8	2
Orthophosphate (mg/L)	0.0001 ± 0.000	0.022 ± 0.021	0.018 ± 0.019	0.008 ± 0.009	0.012 ± 0.012	0.003 ± 0.006	0.010 ± 0.01	0.038 ± 0.065	–	–
Fluorides (mg/L)	0.177 ± 0.078	0.124 ± 0.056	0.111 ± 0.075	0.015 ± 0.011	0.02 ± 0.013	0.021 ± 0.014	0.029 ± 0.018	0.046 ± 0.031	–	0.2
Aluminum (mg/L)	0.005 ± 0.005	0.015 ± 0.01[c,d]	0.003 ± 0.004	0.007 ± 0.009	0.005 ± 0.003	0.004 ± 0.002	0.009 ± 0.014	0.004 ± 0.003	0.01	0.01
Lead (mg/L)	0.029 ± 0.018	0.003 ± 0.004[c]	0.002 ± 0.003	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.003 ± 0.001	0.005	–
Cadmium (mg/L)	0.058 ± 0.125	0.0003 ± 0.001[c]	0.0001 ± 0.0004	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.0007 ± 0.001	0.001	–
Zinc (mg/L)	0.015 ± 0.014	0.014 ± 0.006	0.005 ± 0.005	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.003 ± 0.002	0.1	0.1
Copper (mg/L)	0.203 ± 0.15[c]	0.0625 ± 0.034	0.004 ± 0.004	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.0004 ± 0.001	0.003 ± 0.002	0.1	–
Total iron (mg/L)	0.022 ± 0.017	0.006 ± 0.007	0.010 ± 0.011	0.002 ± 0.003	0.006 ± 0.005	0.008 ± 0.008	0.095 ± 0.11	0.004 ± 0.002	–	–

[a]Association for the Advancement of Medical Instrumentation (AAMI);
[b]European Pharmacopoeia standards for HD water (9th edition 2017);
[c]Significant differences between concentration of parameters with the Association for the Advancement of Medical Instrumentation (AAMI) standards (*P*-value < 0.05);
[d]Significant differences between concentration of parameters with the European Pharmacopoeia (EPh) (9th edition 2017) (*P*-value < 0.05).

Table 3
Rejection rates of chemical parameters

Parameters	Rejection rate %							
	Center No. 1	Center No. 2	Center No. 3	Center No. 4	Center No. 5	Center No. 6	Center No. 7	Center No. 8
pH	18.7	3.4	8.8	13.6	12.9	15.0	10.0	13.9
Conductivity	98.1	95.0	94.1	98.1	97.1	93.8	76.6	94.8
Free chlorine	40.4	73.8	71.2	86.6	79.3	100.0	90.1	80.6
Total chlorine	55.0	62.2	65.6	87.6	63.5	100.0	93.9	77.3
Chlorides	90.9	98.5	95.5	96.1	97.6	98.0	61.8	97.3
Nitrite	51.6	74.3	64.5	88.8	85.6	100.0	90.5	44.3
Nitrate (as N)	93.0	88.1	82.6	90.0	94.2	91.9	91.4	91.5
Calcium	99.8	99.2	95.2	99.1	99.8	99.9	96.9	99.9
Magnesium	99.6	99.6	94.0	99.6	99.9	99.9	71.1	99.6
Total hardness	99.8	99.4	96.4	99.4	99.8	99.9	92.7	99.9
Sulfate	98.6	90.0	80.8	90.5	98.2	96.8	62.9	96.8
Ammonium	63.1	53.6	94.4	54.3	63.9	73.7	56.5	35.9
Oxidizable substances	55.4	59.7	75.8	78.2	66.3	72.0	61.7	59.4
Sodium	99.8	94.2	82.8	92.6	83.2	89.2	85.4	58.1
Potassium	98.9	93.3	96.5	98.7	100.0	99.3	21.9	69.5
Phosphates	91.5	53.6	56.0	55.7	49.0	67.5	43.4	75.4
Fluorides	40.5	60.5	57.0	83.9	88.4	88.9	63.4	90.5
Aluminum	53.8	76.6	87.1	83.4	91.9	89.6	82.2	85.1
Lead	18.7	61.0	74.2	100.0	–	–	–	50.3
Cadmium	8.0[a]	66.7	71.3	–	–	–	–	69.6
Zinc	41.5	53.0	70.9	100.0	100.0	100.0	100.0	84.2
Copper	22.8	80.3	98.7	100.0	–	100.0	98.9	98.2
Total iron	33.9	80.2	75.2	93.8	84.7	84.2	45.5	58.9

[a]There was no significant difference between the concentration of analyzed chemical parameters in municipal drinking water and HD water ($p > 0.05$) $P = 0.397$.

Table 4
Microbiological parameters of municipal drinking water from the eight HD centers

Parameters	Algeria							France	Limits	
	Center No. 1	Center No. 2	Center No. 3	Center No. 4	Center No. 5	Center No. 6	Center No. 7	Center No. 8	Algerian limits[a]	French limits[b]
Total microbial counts (TMCs) 22°C CFU/mL	8.96 ± 22.98	38.28 ± 41.52	42.44 ± 46.35	46.36 ± 133.68	0.84 ± 2.25	1.16 ± 2.75	518.80 ± 188.82	16.92 ± 21.05	–	–
Total microbial counts (TMCs) 37°C CFU/mL	11.8 ± 15.85	9.00 ± 23.72	16.12 ± 41.48	50.00 ± 136.19	1.60 ± 3.63	2.84 ± 6.09	132.20 ± 39.03	21.76 ± 22.43	–	–
Fecal coliforms CFU/100 mL	21.52 ± 14.88[c]	0.00 ± 0.00	0.12 ± 0.60[c]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00	0.00
Sulfite-reducing *Clostridium* CFU/20 mL	1.44 ± 1.69[c]	0.40 ± 2.00[c]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00	0.00
Enterococcus CFU/100 mL	8.36 ± 8.17[c]	0.80 ± 2.29[c]	0.68 ± 2.84[c]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00	0.00
Total coliforms CFU/100 mL	20.08 ± 13.64[c]	5.272 ± 8.93[c]	5.76 ± 9.93[c]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	31.48 ± 10.83[c]	0.08 ± 0.40[c]	0.00	0.00

[a]Official Journal of the Algerian Republic, N°13 (2014);
[b]Official Journal of the French Republic, NOR: SANP0720201A (2007);
[c]Significant differences between concentration of parameters with the Algerian Standards for Municipal Drinking Water. Official Journal N°13 (2014) ($p < 0.05$).

Table 5
Main values of microbiological parameters of HD water from eight HD centers

Parameters	Algeria							France	Limits	
	Center No. 1	Center No. 2	Center No. 3	Center No. 4	Center No. 5	Center No. 6	Center No. 7	Center No. 8	AAMI limits[a]	EPh limits[b]
Total microbial counts (TMCs) 22°C CFU/mL	9.96 ± 15.79	23.92 ± 29.42	22.32 ± 25.14	1.56 ± 3.44	1.96 ± 5.56	0.80 ± 2.55	288.00 ± 132.07[c,d]	0.24 ± 0.83	≤200	≤100
Total microbial counts (TMCs) 37°C CFU/mL	5.20 ± 4.42	4.88 ± 6.83	3.76 ± 4.51	2.36 ± 4.11	3.00 ± 6.92	1.96 ± 4.81	62.20 ± 26.38	3.20 ± 10.10	≤200	≤100
Fecal coliforms CFU/100 mL	1.00 ± 1.83	0.00 ± 0.00	1.008 ± 4.60	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	–	–
Sulfite-reducing *Clostridium* CFU/20 mL	0.44 ± 2.20	0.00 ± 0.00	0.40 ± 2.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	–	–
Enterococcus CFU/100 mL	0.00 ± 0.00	0.00 ± 0.00	0.60 ± 3.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	–	–
Total coliforms CFU/100 mL	3.2 ± 3.39	3.12 ± 8.59	6.68 ± 29.91	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	9.00 ± 6.28	0.36 ± 1.15	–	–

[a]Association for the Advancement of Medical Instrumentation (AAMI);
[b]European Pharmacopoeia standards for HD water (9th edition 2017);
[c]Significant differences between concentration of parameters with the Association for the Advancement of Medical Instrumentation (AAMI) standards ($p < 0.05$);
[d]Significant differences between concentration of parameters with the European Pharmacopoeia (EPh) (9th edition 2017) ($p < 0.05$).

dialysate samples respectively across the 7 Algerian dialysis units. A comparable rate of nonconformity was also registered by Mime et al. [4] in a dialysis center located at the center of Algeria.

Similar trends were observed by Humudat et al. [34] who reported that 44% of dialysis water samples from major hospitals in Baghdad (Iraq) exceeded the international standards for endotoxin (>0.25 EU/mL).In a study conducted in the state of São Paulo State in Brazil, between 2010 to 2016, the authors reported high percentages of noncompliance for endotoxins varying from 16.7% to 93.8% [35]. Other similar investigations performed by Jesus et al. [36] described endotoxin contamination in 77% of water samples using LAL testing. The different results in terms of bacterial counts and endotoxin levels could be explained by the origin of tap water that supplied the dialysis unit, the design of the distribution system, type of materials, and differences in methodologies used for bacteriological tests as reported by Abbass et al. [37], Morghad et al. [30] and Anversa et al. [31].

Various reports have revealed the appearance of chronic pyrogenic and inflammatory reactions among HD patients although a tolerable level of bacterial contamination was detected in HD water [38]. In an important finding, investigations have shown that endotoxin contaminants, found in low amounts and being insufficient to cause febrile reactions, could decrease the response of patients to erythropoietin treatment and adversely affect their health [39]. Similarly, in study conducted in two dialysis centers in Chile, a variety of bacteria isolated from HD water and RO membranes showed high resistance to various antibiotics namely ampicillin, chloramphenicol, and cefotaxime [1]. Another research, undertaken by Hasegawa et al. [40] in Japan reported that the all-cause mortality rate increased by approximately 28% among HD patients when the level of endotoxins in dialysis fluids was ≥0.1 EU/mL. Due to the weakened immune system of ESRD patients, the presence of bacteria and/or endotoxins, even at low levels, could be harmful with a potential risk of infections, hospitalization, and death among dialysis patients. This indicates an extremely urgent need to improve disinfection protocols and the frequency of microbiological monitoring for treatment quality and safety.

4. Conclusions

Based on the results obtained in this research, the quality of HD water, produced in many centers, was not suitable to ensure the efficacy of the therapy. Therefore, immediate actions should be taken to ensure water quality, such as regular maintenance and internal quality controls. In addition, materials, and chemicals, including regenerants and corrosion inhibitors that are in direct contact with the water, should be continuously monitored for their quality and suitability. Any contamination of the dialysis water, even minor, can affect the quality of the dialysate and be harmful to the patient. Hence, the quality of the dialysis fluid should be kept as high as possible since it plays a vital role in the safety and well-being of patients.

The present study revealed alarming and worrying results regarding the quality of water when some HD centers are still utilizing water that does not meet international standards and limits. The current outcomes highlight the importance of upgrading water quality management practices in the dialysis centers. Regular monitoring of dialysis fluid quality, frequent disinfection of the water treatment system and regular maintenance, developing national standards for dialysis water should be considered to ensure safety of hemodialysis therapy.

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Conflicts of interest

Authors declare having no conflict of interest regarding this study.

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